

# This Month in *AJP*

## ***Cytokeratin 17 and 5 Are Prognostic Markers for Node-Negative Breast Carcinomas with Poor Clinical Outcome***

Important prognostic factors in breast carcinoma include tumor size and grade, lymph node status, and the expression of hormone and growth factor receptors. Nevertheless, it is difficult to provide accurate prognosis for individual patients, given the phenotypic variability of tumors within a single category. A recent analysis of breast carcinoma specimens using DNA microarrays, revealed that among patients placed in five groups, patients of two subgroups had a poor prognosis. These groups were characterized by high expression of Her2/neu or of the genes for cytokeratins 5 and 17. As a follow-up of this study, van de Rijn et al (*Am J Pathol* 2002, 161:1991–1996) analyzed 611 paraffin-embedded breast tumor samples using tissue microarrays. Immunohistochemical analysis of cytokeratin 17 and/or cytokeratin 5/6 revealed that expression of these markers was associated with poor clinical outcome. Most importantly, expression of these cytokeratins in node-negative breast carcinoma was a prognostic marker independent of tumor size and grade.

## ***Targeted Inactivation of Guanylin Leads to Enhanced Cell Proliferation in the Intestinal Epithelium***

Secretion of heat stable enterotoxin (STa) by enteric *Escherichia coli* is an important cause of diarrhea, particularly in infants and travelers. Guanylin is a peptide secreted by small and large intestine epithelia, which is highly homologous to STa. Both STa and guanylin bind to the guanylate cyclase C receptor (GC-G) in the endocyte brush border, initiating a signal transduction cascade that culminates with activation of the cystic fibrosis transmembrane conductance regulator (CFTR). The structural similarities between STa and guanylin led to the hypothesis that guanylin has a major role in intestinal fluid transport. Nevertheless, data in the literature suggest that the protein may also have a role in intestinal cell replication. Steinbrecher et al (*Am J Pathol* 2002, 161:2169–2178) investigated intestinal epithelium abnormalities in mice with targeted inactivation of the guanylin gene. The animals developed and grew normally without evidence of alterations in intestinal absorption. However, these mice had a significant increase in the rate of proliferation of colonic epithelial cells, without a change in apoptosis, which was associated with a decrease in GMP. These results may explain the association between decreased expression of guanylin and the development of human and mouse intestinal adenomas.

## ***Osteopontin Inhibits Ectopic Calcification***

Blood vessels, heart valves, and the kidney are highly susceptible to calcium deposition (ectopic calcification). Calcification of atherosclerotic plaques is generally correlated with ischemic episodes in peripheral vessels and the heart. Calcific aortic stenosis is characterized by mineralization of valve leaflets leading to mechanical failure. There are many similarities between the types of proteins involved in cardiovascular calcification and bone mineralization. Mice deficient of matrix GLA protein become highly susceptible to ectopic calcification and generally die of aortic rupture at about 2 months life. Osteopontin is a phosphoprotein normally found in bone, teeth, and epithelial linings that is also deposited in foci of ectopic calcification, including aortic valves and atherosclerotic plaques. Steitz et al (*Am J Pathol* 2002, 161:2035–2046) report that osteopontin is an inhibitor of ectopic calcification. Both *in vivo* and *in vitro* studies suggest that osteopontin can both inhibit mineral deposition and promote mineral dissolution. The data demonstrate that osteopontin has an important role in preventing ectopic calcification.

## ***Regulation of Angiogenesis by Homeobox (Hox) Genes: HoxD10 Maintains Quiescence of Endothelial Cells and Inhibits Angiogenesis***

Angiogenesis is essential for wound healing but also contributes to tumor growth. During tumor angiogenesis, quiescent endothelial cells replicate and produce proteases that degrade the extracellular matrix as well as adhesion molecules that permit cell migration and formation of vascular sprouts. Vertebrate Hox genes are clustered in four linkage groups located on four different chromosomes. HoxD3 and HoxB3 expression is known to increase angiogenesis. HoxD3 increases the expression of  $\alpha v\beta 3$  integrin and urokinase plasminogen activator while HoxB3 facilitates capillary morphogenesis. Myers et al (*Am J Pathol* 2002, 161:2099–2109) reasoned that other Hox genes might be expressed in endothelial cells to maintain their quiescence. They report that HoxD10 expression is higher in quiescent than angiogenic endothelium and that its sustained expression blocked VEGF and bFGF-induced angiogenesis. Furthermore, human

endothelial cells that overexpress HoxD10 failed to form new vessels after implantation in mice. The results show that different Hox genes have opposite effects on angiogenesis and that HoxD10 activity plays a role in maintaining quiescence of endothelial cells.

### ***Amyloid Precursor Protein Is Involved in Cataract Production in Down Syndrome and Age-Related Lens Defects***

Down syndrome (DS; trisomy 21) patients have premature aging and develop Alzheimer's disease with very high frequency. A high proportion of DS patients develop cataracts that may start during childhood. The gene for the amyloid precursor protein (A $\beta$ PP) implicated in Alzheimer's disease is located on human chromosome 21 (mouse chromosome 16), the same chromosome that is duplicated in DS. Expression of this protein is elevated in brains of DS patients. Previous work has shown that A $\beta$ PP and  $\beta$ -amyloid peptides (A $\beta$ ) increases in cortical fiber cells of cultured lenses exposed to oxidative stress. Frederikse and Ren (*Am J Pathol* 2002, 161:1985–1990) studied lenses of transgenic mice that express one copy of the human A $\beta$ PP gene locus containing all exons and introns and most of the 5' promoter and 3' flanking regions, allowing for alternative splicing of the gene in mouse tissues. These mice exhibited fiber cell membrane abnormalities similar to those of human cataracts as well as age-related lens degeneration. The data clearly demonstrate that A $\beta$ PP is a key element in the development of fiber cell formation and early-onset cataracts in DS. Moreover, the results suggest that A $\beta$ PP and other factors involved in Alzheimer's disease contribute to the pathogenesis of age-related cataracts in the general population.

### ***Nipah Virus Infection: A New Human Disease***

In 1998–1999 there was an outbreak of an unrecognized paramyxovirus infection among pig handlers in Malaysia and Singapore. The disease was believed to have spread by transportation of infected pigs to farms and slaughterhouses. Most patients presented with acute encephalitis and had a high mortality rate of approximately 40%. Viral isolation and sequencing indicated that the disease was caused by a previously unknown virus which was given the name of Nipah virus (the virus was first isolated from a Nipah River village). Wong et al (*Am J Pathol* 2002, 161:2153–2167) report on autopsy findings of 32 patients who died with Nipah virus infection. Diagnosis of the disease could be established by a combination of immunohistochemistry and serology. The main finding consisted of systemic vasculitis and thrombosis, with endothelial cell damage and necrosis that was particularly intense in the central nervous system. Blood vessel endothelial and smooth muscle cells as well as neurons contained viral antigens. This report is the first complete description of the histopathology of this new human disease.